

REMARKS

Upon entry of the present amendment, claims 1, 6-8 and 17 are pending. Claims 2-5, 9-16 and 18-25 have been cancelled herein without prejudice or disclaimer. Claims 1 and 6-7 have been amended to recite specific splice variants of the isolated lubricating gene products of the megakaryocyte stimulating factor (MSF) gene and an O-linked oligosaccharide moiety. Support for the claim amendments presented herein is found throughout the specification. For example, support for these claim amendments is found at least at page 2, lines 15-28; at page 5, lines 7-13; in Table 3 on page 11; at page 11, line 4 through page 12, line 15; at page 26, line 26 through page 28, line 6; in Example 2 at pages 33-34; and in Table 10 at page 41. Claim 17 has been amended to maintain proper claim dependency and antecedent basis in light of the amendments to claims 1, 6, 7 and 8. Accordingly, no new matter has been added by the amendments presented herein.

I. Objections to the Specification

The Examiner has objected to Tables 1 and 2 because the sequence identifiers appear at the end of the Table. As suggested by the Examiner, these tables have been amended to include the sequence identifiers at the top of each table, next to the title. Accordingly, Applicant believes that the grounds for this objection have been obviated, and this objection should be withdrawn.

The Examiner has also objected to the recitation of "(Figs. 2A and 2B)" at page 39, lines 6-7 of the as-filed specification. The specification has been amended to replace the reference to "Figs. 2A and 2B" with "Fig. 2". Accordingly, the Examiner should withdraw this objection.

II. Claim Rejections Under 35 U.S.C. § 101

Claims 1-8 and 17 have been rejected under 35 U.S.C. §101. According to the Examiner, the claimed invention is directed to non-statutory subject matter, because the term "lubricating polypeptide" reads on the natural, non-patentable, state of the lubricating polypeptide.

As suggested by the Examiner, the independent claims have been amended to recite a composition that comprises an isolated lubricating MSF gene product. Thus, the amended claims are directed to lubricating gene products removed from the natural environment. Accordingly, Applicant believes that this rejection has been obviated and should be withdrawn.

III. Claim Rejections Under 35 U.S.C. § 112, First Paragraph

Claims 1-8 and 17 have been rejected under 35 U.S.C. § 112, first paragraph for lack of enablement. According to the Examiner, the specification “does not reasonably provide enablement for any lubricating polypeptide that comprises an amino acid sequence of a variant or a fragment of SEQ ID NO:1.” (Office Action, page 3).

The claims have been amended herein to recite compositions that contain lubricating MSF gene products that consist of specific amino acid residues of SEQ ID NO:1 and at least one O-linked oligosaccharide. In particular, amended claim 1 recites a composition that includes an isolated lubricating MSF gene product that consists of amino acid residues 67-106 and 200-1140 of SEQ ID NO:1 and at least one O-linked oligosaccharide. The isolated lubricating MSF gene product recited by claim 6, as amended, consists of amino acids 1-25, 67-106, and 200-1404 of SEQ ID NO:1 and at least one O-linked oligosaccharide, while the isolated lubricating MSF gene product of amended claim 7 consists of amino acids 1-156 and 200-1404 of SEQ ID NO:1 and at least one O-linked oligosaccharide. The isolated lubricating MSF gene product of amended claim 8 consists of amino acids 1-106 and 200-1404 and at least one O-linked oligosaccharide.

Thus, the amended claims are not directed to any variant or fragment of SEQ ID NO:1. Rather, these claims recite several specific splice variant gene products, the amino acid sequence of which consist of the specific amino acid residues of SEQ ID NO:1 that correspond to a subset of MSF exons shown in Figures 1A and 1B. Applicant submits that the specification provides ample guidance with regard to making and using the compositions defined by the amended claims. Thus, undue experimentation would not be required to practice the claimed invention. Accordingly, Applicant requests that the Examiner withdraw this rejection.

III. Claim Rejections Under 35 U.S.C. § 112, Second Paragraph

Claims 1-8 and 17 have been rejected under 35 U.S.C. §112, second paragraph as being indefinite. According to the Examiner, original claims 1, 2, 3, 6 and 17 are indefinite because it is not clear whether the sequence identity recited by the claim is to the defined residues or to the complete sequence of SEQ ID NO:1.

Claims 2-5 have been cancelled, thereby rendering any rejections of these claims moot. In addition, claims 1, 6, 7 and 8 have been amended to recite compositions that recite a specific splice variant of an isolated lubricating MSF gene product and at least one O-linked oligosaccharide. In other words, the claims clearly require that the claimed isolated lubricating MSF gene products consist of only the defined residues, rather than the entire amino acid sequence of SEQ ID NO:1.

For example, claim 1, as amended, is directed to a composition that includes an isolated lubricating MSF gene product that consists of amino acid residues 67-106 and 200-1140 of SEQ ID NO:1 and at least one O-linked oligosaccharide. Claim 6 has been written as an independent claim that recites a composition that contains an isolated lubricating MSF gene product that consists of amino acids 1-25, 67-106, and 200-1404 of SEQ ID NO:1 and at least one O-linked oligosaccharide, while claim 7 has been rewritten as an independent claim that is directed to a composition that includes an isolated lubricating MSF gene product that consists of amino acids 1-156 and 200-1404 of SEQ ID NO:1 and at least one O-linked oligosaccharide. Claim 8, also rewritten as an independent claim, recites a composition that contains an isolated lubricating MSF gene product that consists of amino acids 1-106 and 200-1404 and at least one O-linked oligosaccharide.

Thus, these amended claims clearly recite that the sequence identity consists of the defined amino acid residues set forth in amended claims 1, 6, 7 and 8, as opposed to the complete sequence of SEQ ID NO:1. As such, Applicant submits that the amended claims are clear and definite, and this rejection should be withdrawn.

Moreover, with regard to the Examiner's rejections and warnings under 37 CFR 1.75, Applicant notes that claims 1, 6, 7 and 8, as amended, recite compositions that contain different splice variants of an isolated lubricated MSF gene product. In other words, the amended claims have different claim scopes, as the MSF gene products contained in the compositions of amended claims 1, 6, 7 and 8, have different amino acid sequences. Thus, the amended claims

are not "substantial duplicates", nor do these claims "cover the same thing". Accordingly, withdrawal of these rejections is requested.

IV. Claim Rejections Under 35 U.S.C. § 102

Claims 2 and 8 have been rejected under 35 U.S.C. § 102(b) as being anticipated by Flannery *et al.*, Biochem. and Biophys. Res. Comm., vol. 254:535-41 (1999) ("Flannery"). According to the Examiner, Flannery discloses an articular cartilage superficial zone protein (SZP), which contains large and small mucin-like repeat domains "likely to be substituted with O-linked oligosaccharides which would impart lubricating properties to SZP". (Office Action, page 7).

Claim 2 has been cancelled, thereby rendering any rejections of this claim moot. Claim 8, as amended herein, is directed to a composition comprising an isolated lubricating MSF gene product consisting of amino acids 1-106 and 200-1404 and at least one O-linked oligosaccharide.

Thus, amended claim 8 requires that the isolated lubricating MSF gene product of the claimed compositions contain amino acids 1-106 and 200-1404. In contrast to the lubricating MSF gene products of the claimed invention, the SZP proteins of the Flannery reference do not contain amino acids that correspond to residues 103-1002 of SEQ ID NO:1 (*see* Flannery, Figure 1 on page 537). Accordingly, this reference fails to disclose every element of the claimed compositions, and this rejection should be withdrawn.

V. Claim Rejections Under 35 U.S.C. § 103

Claims 1-8 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Flannery in view of Turner *et al.*, U.S. Patent No. 6,433,142 ("Turner").

As described above, each of the isolated lubricating MSF gene products recited by the amended claims explicitly require the presence of at least amino acids 200-1140 of SEQ ID NO:1, *i.e.*, the amino acids that correspond to Exon 6 of the human megakaryocyte stimulating factor MSF gene sequence shown in Table 2 of the instant application. Moreover, each of the amended claims requires that the lubricating MSF gene products in the claimed compositions lack amino acid residues that correspond to at least one exon of the MSF gene sequence. For example, amended claim 1 recites a composition containing a lubricating MSF gene product that

consists of the amino acid residues that correspond to Exons 3 and 6 of the MSF gene, but lacks the amino acid residues that correspond to Exons 1, 2, 4, 5, and 7-12. Amended claim 6 is directed to a composition containing a lubricating MSF gene product that consists of the amino acid residues that correspond to Exons 1, 3 and 6-12 of the MSF gene, but lacks the amino acid residues that correspond to Exons 2, 4 and 5. Claim 7, as amended, recites a composition containing a lubricating MSF gene product that consists of the amino acid residues that correspond to Exons 1-4 and 6-12 of the MSF gene, but lacks the amino acid residues that correspond to Exon 5. Amended claim 8 is directed to a composition containing a lubricating MSF gene product that consists of the amino acid residues that correspond to Exons 1-3 and 6-12 of the MSF gene, but lacks the amino acid residues that correspond to Exons 4 and 5.

Unlike the lubricating MSF gene products of the claimed invention, the SZP proteins described in the Flannery reference do not contain amino acids that correspond to residues 103-1002 of SEQ ID NO:1. Moreover, there is no teaching or suggestion in this reference that would motivate a person of ordinary skill in the art to modify the Flannery proteins to include amino acids 103-1002 of SEQ ID NO:1. Accordingly, the lubricating MSF gene products of the claimed compositions recited by the amended claims are not obvious in view of the Flannery reference.

In addition, the claimed lubricating MSF gene products are not obvious in view of the Turner reference. One of ordinary skill in the art would not be motivated by the teachings of the Turner reference to glycosylate the MSF proteins described therein, as the Turner proteins and the isolated lubricating MSF gene products of the claimed invention have different uses. The glycosylated lubricating MSF gene products of the claimed invention are used to lubricate a joint or other biological boundary. The Turner proteins, in contrast, were isolated from urine and used to stimulate the growth and development of colonies of megakaryocyte cells. Thus, there is no need for the Turner MSF proteins to exhibit lubricating properties. Accordingly, a person of ordinary skill in the art would not be motivated by the teachings of the Turner reference to modify the MSF proteins to include an O-linked glycan.

Applicant also submits that a person of ordinary skill in the art would have no motivation to combine the teachings of the Flannery reference with the teachings of the Turner reference to produce lubricating MSF gene products that include at least one O-linked oligosaccharide. A *prima facie* case of obviousness requires some suggestion or motivation, either in the references

themselves or in the knowledge generally available in the art, to modify the reference or to combine reference teachings. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art and not based on applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991). *See also* MPEP 706.02(j). Any attempt to suggest that it would have been obvious to a person of ordinary skill in the art to glycosylate the MSF proteins described by the Turner reference is an improper application of hindsight based on the disclosure in the instant application. Thus, the Examiner has failed to establish a *prima facie* case of obviousness.

Furthermore, the claims require the MSF gene products be "lubricating", *i.e.*, reduce a coefficient of friction. First, Flannery's description of the presence of an O-linked oligosaccharide and any lubricating activity of SZP is, at best, speculative:

The mucin-like domains are likely to be substituted with O-linked oligosaccharides which would impart lubricating properties to SZP which in part accumulates at the articular cartilage-synovial fluid interface. (Flannery at page 535, col. 1)

Flannery does not state that SZP contains an O-linked oligosaccharide, he simply states that the mucin-like domains could serve as a substrate for such a carbohydrate linkage, which, if it were present, could impart lubricating property.

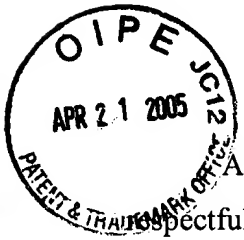
Second, the speculation that Flannery's SZP may have lubricating properties has now been shown to be unsupported. Caligaris *et al.* (Osteoarthritis and Cartilage (2004) 12, 947-955; copy attached hereto in the APPENDIX) states:

Coupled with the histological confirmation that SZP was present in intact specimens and absent in microtomed specimens, and the consistency between the results of experiment 1 (4.4 N normal load) and experiment 2 (22.2 N normal load), these results do not support the hypothesis that the topmost superficial zone of cartilage, where SZP is localized, has special properties which reduce the coefficient of friction at the articular surface. (emphasis added).

Thus, neither of the cited references describe a lubricating MSF gene product and one of skill in the art would not be motivated to make an alternative splice variant MSF gene product with an O-linked oligosaccharide and concomitant lubricating properties.

Accordingly, withdrawal of this rejection is requested.

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CONCLUSION

Applicant submits that the application is in condition for allowance and such action is respectfully requested. Should any questions or issues arise concerning the application, the Examiner is encouraged to contact the undersigned at the telephone number provided below.

Respectfully submitted,

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Attachment:

-- Courtesy copy of Caligaris *et al.*, Osteoarthritis and Cartilage, vol. 12:947-955 (2004) (9 pgs.)

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